WE CLAIM:

1. An improved method for modifying the genome of a embryonic stem cell so as to contain, in the genome thereof, a xenogeneic DNA segment of at least 100 kb which method comprises:

combining under fusing conditions embryonic stem cells and yeast spheroplasts, said spheroplasts containing a yeast artificial chromosome (YAC) comprising said xenogeneic DNA segment and including a marker for selection, whereby said xenogeneic DNA segment becomes integrated into the genome of said embryonic stem cells; and

selecting for an embryonic stem cell carrying said xenogeneic DNA segment by means of the marker.

2. An improved method for producing a modified nonhuman animal, said animal having a xenogeneic DNA segment of at least 100 kb stably integrated into the genome of at least some cells of said animal, said method comprising:

combining under fusing conditions embryonic stem cells of said animal and yeast spheroplasts, said spheroplasts containing a yeast artificial chromosome (YAC) comprising said xenogeneic DNA segment and including a marker for selection, whereby said xenogeneic DNA segment becomes integrated into the genome of said embryonic stem cells;

selecting for embryonic stem cells carrying said xenogeneic DNA segment by means of the marker; and

transferring said embryonic cells into a host blastocyst, implanting said blastocyst in a pseudopregnant animal recipient, and allowing said blastocyst to develop to term to produce a chimeric animal carrying said xenogeneic DNA segment integrated into the genome of at least some cells of said animal.

3. An improved method for producing a modified nonhuman animal, said animal having a xenogeneic DNA segment of at least 100 kb stably integrated into the genome of said animal, said method comprising:

combining under fusing conditions embryonic stem cells of said animal and yeast spheroplasts, said spheroplasts containing a yeast artificial chromosome (YAC) comprising said xenogeneic DNA segment and including a marker for selection, whereby said xenogeneic DNA segment becomes integrated into the genome of said embryonic stem cells;

selecting for embryonic stem cells carrying said xenogeneic DNA segment by means of the marker;

transferring said embryonic cells into a host blastocyst and implanting said blastocyst in a pseudopregnant animal recipient, and allowing said blastocyst to develop to term to produce a chimeric animal carrying said xenogeneic DNA segment; and

mating said chimeric animal with an animal of the same species to produce said modified animal carrying said xenogeneic DNA segment.

4. A method according to any of claims 1, 2 or 3, wherein said marker is the HPRT gene and said embryonic stem cells are HPRT deficient.

5. A method according to any of claims 1, 2 or 3, wherein said xenogeneic DNA is human DNA, and/or wherein said xenogeneic DNA is immunoglobulin DNA in substantially intact form.

6. Embryonic stem cells comprising a genome modified according to the method of claims 1, 4 or 5.

7. A modified animal produced according to the method of claims 2, 3, 4 or 5.

8. The stem cells of claim 6 which are of a rodent.

9. The stem cells of claim 8 which are murine.

10. The animal of claim 7 which is rodent.

11. The animal of claim 10 which is a mouse.